

TABLE 1-continued

SEQ ID NO: ODN SEQUENCE	BACKBONE
176 tcctgacgtccccctggcggtccccctgtcgct	o
177 tcctgtcgctccctgtcgctccctgtcgct	o
178 tcctggcgggaaagt	o
179 tcctgazgttgaagt	o
180 tcctgacgttgaagt	o
181 tcctaggttgaagt	o
182 tccagacgttgaagt	o
183 tcctgacggggaaagt	o
184 tcctggcggtgaagt	o
185 ggctccggggaggaaattttgtctat	o
186 atagaaaaaaattccctcccccggagcc	o
187 tccatgagcttccctgtcgct	rna
188 tcgtcgatgttcctcccgcttc	so
189 tcgtcgatgttcctcccgcttc regtgcgtgttcgttccgttccgtt	s20
190 tcgagacatggcaacaatcatcg	o
191 cagattgtgcattgtctcg	o
192 tccatgtcggtccctgtcg	o
193 gcgatgtcggtccctgtcg	o
194 gcgatgtcggtccctgtcg	o
195 tccatgtcggtcccgccg	o
196 tccatgtcggtccctgccc	o
197 tccatgtcggtccctgtcg	o
198 gcgccgggcggcgccgcgc	o
199 atcaggaacgtcatggaaagc	o
200 tccatgagcttccctgtcg	p-ethoxy
201 tcaacgtt	p-ethoxy
202 tcaagctt	p-ethoxy
203 tcctgtcggtccctgtcg	s
204 tccatgtcggttttgcgtt	s
205 tcctgtcggtccctgtcg	s
206 tcctgtcggtccctgtcg	s
207 btccatccatgacgtccatgtcgatgttcca	os
208 tcctgtcggttttgcgtt	s
209 tcgtcggtgtcccggttctt	s
210 tcgtcggtgtcccggttctt	s
211 tcgtcggtgttgcgttctt	s
212 tcctgtcggtccctgtcggtggaaacgacagg	o
213 tcctgtcggtccctgtcggttcaacgtcaggaaacgacagg	o
214 ggggtgtcggtttttgggggg	sos
215 ggggtgtcggtttttgggggg	sos
216 tccggcgttgaagt	o
217 tccggacgggtgaagt	o
218 tcccgccgttgaagt	o
219 tccagacgggtgaagt	o
220 tcccgacgggtgaagt	o
221 tccagagcttgaagt	o
222 tccatgtcggtccctgtcg	s
223 tccatgacgttccctgacgtt	sos
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241 tccatgatttccctgtcgatgtt	s
242 tccatgacgttccatcgatgttccatcg	s
243 ggccggcgccggccggccgg	o
244 tccacacgttttcgacgtt	s
245 tcgtcggtgtcggtcg	s
246 tcgtcggttttgcgttgcgtt	s
247 tcgtcggtgtcggtcg	s
248 ggtgtcggtgtcggtcg	s
249 czggczggczggczccq	o

TABLE 1-continued

TABLE 1-continued

SEQ ID NO:	ODN SEQUENCE	BACKBONE
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325	tctcgacgttgaagt	s
326	tcttcggcggtgaagt	s
327	tctgtcgacggtgaagt	s
328	tctgtcgatgtgaagt	s
329	tcttcggcggtgaagt	s
330	aaaatctgtgtttttaaaaaa	sos
331	gatccaggatcacagtgcacgtggcagaatctggat	o
332	gatccaggatgtccaggtaactgtgactggat	o
333	gatccaggatcacagtgactcaagaaatctggat	o
334	gatccaggatgtgtgactcaactgtgactggat	o
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351	tcgtcggttcccccccccccccb	o
352	tcgtcggttttgcgtttgtcggtb	o
353	tccaggtccttctcagtt	o
354	tzgtcggttttgcgtttgtcggt	o
355	tcctgggggggaagt	s
356	tcttcgaaaggaaagt	s
357	tcgtcggttcccccccccc	s
358	tzgtzgtttttzgttttgcgtt	s
359	ggggtaagcttggggggg	sos
360	tcgtcggttcccccccccc	s
361	tcgtcggtcggtt	s2
362	tcgtcggtcggtt	s20
363	tcgtcggtcggtt	os2
364	tcaacgttga	s
365	tcaacgtt	s
366	atagtttccattttttac	
367	aatagtcgcacatcgcgac	o
368	aatagtcgcacatcccgggac	o
369	aatagtcgcacatcccccc	o
370	tcgtcggtttgtcggtttgtcggt	o
371	ctgtcggtttctgtgttttctgt	s
372	ctaaatttttaatttttttaa	s
373	tcgtcggtgtgtcggtgtcggt	s
374	tcgtcggtgtgtcggtttgtt	s
375	accatggacgagctgtttccctc	
376	tcgtcggttttgcgtgcgtt	s
377	ctgtaaagtggatgtggagag	
378	gagaacgcgtggacccctcc	
379	cgggcgactgtatctatcg	
380	gttcttcgataaaacgcggaaaccaggacaacacacacaa	
381	ttctgtgtctgttgcgtgtttccgtttatctgagaac	
382	cacagacacagacccggatagacg	
383	agacagacacacaaacgacccg	
384	gtctgtcccatgtatctcgaa	
385	gctggccacgttaccccccgg	
386	ggggccctatacacaacctggg	
387	ggggccctcgagactgccc	
388	gagaacgcgtggacccctccat	
389	tccatgtcggtttctgtgtct	
390	ctcttgcgacccgttggaaagt	
391	aggtaacaggccaggactacga	
392	accatggacgactgtttccctc	
393	accatggattaccccttccctt	
394	atggaaaggccacgttctc	
395	agcatcaggccaggacatgg	
396	ctcttccaaatgtactttacag	
397	tccctqagacttgcacccaccc	

TABLE 1-continued

SEQ ID NO: ODN SEQUENCE	BACKBONE
471 tcagtcgtgtacttttca	
472 tggttacggctgtccatg	
473 gtctatcgaggactggcgc	
474 cattttacggcgccggcgc	
475 gaggggaccatttacggc	
476 tgtccagccgggggaccat	
477 cgggcttacggcgatgtctg	
478 tggacccctatgtcggtcc	
479 tgtccatgttttagaagc	
480 gtggttacggtcgccat	
481 cctccaaatgaaagaccccc	
482 ttgtacttccatgtgggt	
483 ttccatgtgttccgggtgg	
484 gacttctatgtcggtctg	
485 gagaccgcgtgacccctcgat	
486 ttgccccatatttttagaaac	
487 ttgaactqaggtgggac	
488 ctatcgaggactggcgcc	
489 cttggaggggctccggcg	
490 gctgaacctccatgtgttt	
491 tagaaacacgatttttttagggcagcaca	
492 agatgttctcagataaagcgaa	
493 ttccgcattatctgaaaccatct	
494 gtcccggttgatagaggctgc	
495 gcgcagtcctccatagac	
496 atcgaggactggcgcc	
497 ggtctgtcccatatttttag	sos
498 ttttcaacgttgagggggg	sos
499 ttttcaagcggtgattttt	sos
500 ggggtcaacgttgattttt	sos
501 ggggtttcaacgttttaggggggg	sos sos
502 ggttacggtctgtccatat	
503 ctgtcccatatttttagaca	
504 accatccgtggccatcg	
505 cgtctatcggttcgtgtctg	
506 ggcacatcccacattaaagt	
507 ccaaatatcggtgtcaagcac	
508 gtgttgcaccaccatattttgg	
509 gtgttgcaccatgttttttttt	
510 ggccaaacttcaatgtggggatggcctc	
511 ttccgcgaatggccctcaggatggta	
512 tatagtccctgagactggccacccttcaacaacc	
513 gcacgcctataacaactgggacggga	
514 ctatcgaggactggcgcc	
515 tatcgaggactggcgcc	
516 gatcgaggactggcgcc	
517 ccgaacaggatatacggtatcgac	
518 ttttggggtaacgttgagggggg	
519 ggggtcaacgttgagggggg	sos
520 cgcgcgcgcgcgcgcgc	s
521 ggggcattgtacgttccgggggg	ss
522 ggggcattgtacgttcaaaaaas	s
523 ggggcattgtacgttccgggggg	s
524 ggggcattgtacgttccgggggg	sos
525 aaaaatgtacgttcaaaaaaa	sos
526 aaaaatgtacgttccgggggg	sos
527 ggggcattgtacgttcaaaaaaa	sos
528 accatggacgatctgtttccctc	s
529 gccatggacgaaactgttccctc	s
530 cccccccccccccccccccc	sos
531 ggggggggggggggggggggg	sos
532 gctgtaaaatgtacgtggcc	sos
533 ttccggcggactcttcatt	sos
534 tatgcggcggccggacttat	sos
535 ggggtaaatcgatcagggggg	sos
536 tttgagaacgtggaccc	sos
537 gatcggtatctaattgtcg	sos
538 gtccgttctgtgtgttcc	sos
539 tcgtcgatgtcgatgtcg	sos
540 ctggacccatgtcg	sos
541 gtcgttcaagcggtct	sos
542 ctggacccatgtcg	sos
543 cactgtccatgtcg	sos
544 cgctggacccatgtcg	sos

TABLE 1-continued

SEQ ID NO: ODN SEQUENCE	BACKBONE
545 gctgagctcatgccgtctgc	sos
546 aacgctggacccttccatgtc	sos
547 tgcatggcgatcacagctct	sos
548 cttccatgtcggtctcgat	sos
549 tactttcggatcccttgcg	sos
550 ttccatgtcggtctcgat	sos
551 ctgattgtctctcgat	sos
552 ggcgttattccgtactcgcc	o
553 cctacgttgtatgcggccagct	o
554 ggggttaatcgatgggggggg	o
555 ttcggcgactctccatt	o
556 ttttttttttttttttttt	o
557 ggggttttttttttttttttt	o
558 ttttttttttttttttttttttt	o
559 ggggggggggggggggggg	o
560 aaaaaaaaaaaaaaaaaaaaaa	o
561 ccccccccccccccccccccc	o
562 aaaaacccccccccccccaaaa	o
563 tttgaattcaggactggtaggtttag	o
564 tttgatctcagcggctccaggtag	o
565 aatttctatcggggttctgtgtctgtgtgttttat	o
566 cttagataaaggaaaccagcaacagacacagaageccccatagag	o
567 tttttagagggtcacaatgtctgg	o
568 tttgaattccgttacagaagcgagaagc	o
569 tttggccgcgtacttaatctgagatata	o
570 tttggcccacgagagacagagacacttc	o
571 tttggccgcgttctcgcttctgtacacg	o
572 gagaacgtggacccatccat	s
573 tccatgtcggtctgtatgt	s
574 ctgtcg	s
575 tcgtga	s
576 cgtcga	s
577 agtgct	s
578 ctgtcg	o
579 agtgct	o
580 cgtcga	o
581 tcgtga	o
582 gagaacgcgtccagcttcgat	o
583 gctagacgttaacgtcgat	o
584 gagaacgcgtcgaccctccat	o
585 gagaacgcgtggaccatccat	o
586 gctagaggtagcgat	o
587 gagaacgcgtggacttcat	o
588 tcacgtaacgtctagc	o
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590 atggaaaggtcgagcgatctc	o
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593 gagaacgcgtggatccat	o
594 gagaacgcgtccagcactgt	o
595 tccatgtcggtctgtatgt	o
596 atgtccctgggtccctgtatgt	o
597 gagaacgcgtccacccatccat	o
598 gagaacgcgtggacccttcgat	o
599 batggaaaggccacgttctc	o
600 tcctgt	o
601 tcaacgtt	o
602 aacgtt	o
603 aacgttga	o
604 tcacgtaacccatcgat	o
605 gagaacgcgtggacccttcgat	o
606 gctggaccatccat	o
607 gagaacgcgtggaccatccat	o
608 gagaacgcgtggaccgtccatccat	o
609 aacgttggggcat	o
610 atgcctcaacgtt	o
611 tcaacgttga	o
612 gctggaccatccat	o
613 caacgtt	o
614 acaacgttga	o
615 tcacgt	o
616 tcaagctt	o
617 tcgtca	o
618 aggatatc	o

TABLE 1-continued

SEQ ID NO: ODN SEQUENCE	BACKBONE
619 tagacgtc	o
620 gacgtcat	o
621 ccatagat	o
622 atcgatgt	o
623 atgcgtgt	o
624 ccatgcgt	o
625 agcgctga	o
626 tcaggcgt	o
627 ccttcgt	o
628 gtgcgggggtctccgggc	o
629 gctgtggggcggtctcg	s
630 btaacacgtt	o
631 ftcaacacgtt	o
632 faacgttqa	o
633 tcaacgt	s
634 aacgttg	s
635 cgacga	o
636 tcaacgtt	o
637 tcggta	o
638 agaacgtt	o
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647 gagcaagctggacacctccat	s
648 cgcgta	s
649 cgtacg	s
650 tcacccgt	s
651 caagagatgtcaacaatgca	s
652 acccatcaatagctctgtgc	s
653 ccacatcgat	o
654 tcgacgtc	o
655 ctacgcgt	o
656 taaggcgt	o
657 tgcgaaattcgcg	o
658 atggaaagggtccacgcgttct	o
659 actggacgttagcgtga	o
660 cgccgtgggtctccgggc	o
661 gtgtcgggggtctccgggc	o
662 gtgcgggggtctccgggc	o
663 cgccgtcgccgggttgg	o
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679 aacgttct	o
680 tccgatcg	o
681 tccgtacg	o
682 gctagacgtcaacgtga	o
683 gagaacgttagacccatcatccat	o
684 gagaacgttagacccatcatccat	o
685 actagacgttagtgcgtga	o
686 cacaccttggtaatgtcacgt	o
687 ttcctcatccatggtttatcg	o
688 cgctggaaatccat	o
689 caccacccgttcaatgtcacgt	o
690 gctagacgttagctgaa	o
691 agtgcgttgcagatcg	o
692 ttttcgttttgggttttgtggtt	o

TABLE 1-continued

SEQ ID NO:	ODN SEQUENCE	BACKBONE
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694	ttttgtttgtgggtttgtggtt	
695	accgcatggattctaggcca	s
696	gctagacgttagcgt	o
697	aacgctggacccat	o
698	tcaazgtt	o
699	ccttcgat	o
700	actagacgttagtgtga	s
701	gctagaggtagcgtga	s
702	atggactctccagcgttctc	o
703	atcgactctcgagcgttctc	o
704	gctagacgttagc	o
705	gctagacgt	o
706	agtgcgattcagatcg	o
707	tcagzgtt	o
708	ctgattgctctctcgtagtga	o
709	tzaacgtt	o
710	gagaazgctggaccctccat	o
711	gctagacgttagcgtga	o
712	gtctacttagcgtga	o
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730	atcgacttcacgtcggttctc	o
731	gctagazgttagcgt	o
732	atcgacttcacgtcggttctc	o
733	ggggtaatgcgtcgtgggggg	sos
734	ggctgttatttcgtgactggcc	s
735	ccatgctaacctctagc	o
736	gctagatgttagcgtga	o
737	cgtagccatcggtga	o
738	tccatgctgggtctgtatgct	o
739	atcgacttcacgtcggttctc	o
740	gctagacgttagcgtga	o
741	atcgacttcacgtcggttctc	o
742	aacgctcgacccttcgat	o
743	ctcaacgctggacccttcat	o
744	atcgacttcacgtcggttctc	o
745	gagaatgtcgacccttcat	o
746	tcacgctaacctctgac	o
747	bgagaaacgttcacgtcgat	o
748	bgagcaagctggacccttcat	o
749	cgcttaggttagcgtga	o
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761	gctaggccgttagcgt	o
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763	tccatgtcggtctgtatgct	o
764	atcgacttcacgtcggttctc	o
765	atggaaagggtccacgttctc	o
766	gcatgacgttagcgt	o

TABLE 1-continued

SEQ ID NO:	ODN SEQUENCE	BACKBONE
767	ggggtcaacgttgagggggg	s
768	ggggtcaagtctgggggg	sos
769	cgcgcgcgcgcgcgcgc	o
770	cccccccccccccccccccccccc	s
771	cccccccccccccccccccccccc	s
772	tcgtatgtcgctctgtatct	o
773	gtcaaacgttagcgt	o
774	tccatgtcgatctgtatgt	o
775	tccatgcgggtctgtatgt	o
776	aaaatcaacgtgaaaaaaaa	sos
777	tccataacgttctgtatgt	o
778	tggagggtccccaccggatcgag	o
779	cgtcgtcgtcgtcgtcgt	s
780	ctgtcgctgtcgctgtcg	s
781	gagaacgcgtccgcacccgtat	s
782	gtctatgttagcgt	s
783	gcgtacgttgagct	s
784	tcaatgtcgat	o
785	tcaacgttgat	o
786	tcaacgttgab	o
787	gcaatattgcg	o
788	gcaatattgcg	o
789	atgttgcgaa	o
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791	tcaacgtc	o
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793	gtttttatataattttgg	o
794	tttttgttgcgttttgcgtt	o
795	ttgggggggt	s
796	gggggtgggggt	s
797	ggtgtgttagttttgg	o
798	bgagaaazgtccgcacccgtat	o
799	tcaacgttaacgttaacgtt	o
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801	bgagaaazgtccgcacactgtat	o
802	tcaazgttgcg	o
803	gzaatattgcx	o
804	tgtgtgttttgtcggttttgtgttt	o
805	ctgcgttagacaatttaactgtg	o
806	tccatgtatgtcgatgtatgt	s
807	tgcgtccgtgtcgtacacagctct	s
808	tgcgtcgatcacacagctct	s
809	tgcgtacgtat	s
810	tgcgtct	s
811	cccccccccccccccccccc	s
812	cccccccccccc	s
813	cccccccc	s
814	tgcgtacgtat	sos
815	tgcgtccgtacacagctct	o
816	gagcaacgtggacccctccat	s
817	tcaacgttaacgttaacgttaacgtt	s
818	gagaacgtccgtacccctcgat	s
819	gtccccatttcccgagaggaaat	o
820	ctagcggtgtacgtcatcaagctag	o
821	ctagcttgcgtacgtcagccgttag	o
822	cggctgtacgtcatcaa	s
823	ctgacgtg	o
824	ctgacgtcat	o
825	attcgtatggggggggcgag	o
826	ctcgccccccccgatcgat	o
827	gactgtacgtcgat	o
828	ctagcggtgtacgtcataaagctagc	s
829	ctagcttgcgtacgtcagccgtac	s
830	ctagcggtgtacgtcataaagctagc	s
831	ctagcttgcgtacgtcatcaagctag	s
832	tccaccaacgtgggtctatgt	s
833	gggaatgtaaaatgttttattataag	o
834	tctaaaaaccatctattcttaaccct	o
835	agctcaacgtcatgc	o
836	ttaacgggtgttagcggttattggc	o
837	ttaagaccataccgttaccccg	o
838	gatctatgtatgttagtacgtcgccggatc	o
839	gatccgggtgtactcatcaactagatc	o
840	tccaaagacgttctgtatgt	o

TABLE 1-continued

SEQ ID NO: ODN SEQUENCE	BACKBONE
941 tccatgacgtccctgatgct	o
942 tccaccacgtggctgatgct	o
943 ccacgtggaccccttagc	o
944 tcagaccacgtggccgggttccctga	o
945 tcaggaacacccgaccacgtggctgtf <i>o</i>	o
946 cattttccacggatttccca	o
947 ttccctt t gcaagagact	o
948 tgtatcttctgaaggact	o
949 ataaagcggaaactagcagcagtttc	o
950 gaaactgtctgtatgtttcgctttat	o
951 tgcccaaaaggaaaaatttggttcatacag	o
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958 cttagctgacgtcatcaagctgt	o
959 tctgacgtcatctgacgttggctgacgtct	o
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961 tttaaccttataaaacataactaaaacaaa	o
962 gcgtttttttttgcg	s
963 atatcttaatcaaaaacatataaaaaaa	o
964 tctatcccagggtggttctgttag	o
965 btccatgacgttccgtatgct	o
966 btccatgacgttccgtatgct	o
967 ttttttttttttf	o
968 ttttttttttttf	so
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906 aggggggggggggggggggg	s
907 tgcgtgtgtgtgtgtgtgtgt	s
908 ctctctctctctctctctctct	chimeric
909 ggggtcgcgtcgagggggg	s
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911 tttttttttttttttttttttttt s	
912 tttttttttttttttttttt s	s
913 tttttttttttttttttt s	
914 gctaggggggggggt	

TABLE 1-continued

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918 atggactctggagggggctc	
919 atgaaaggttcaagggggctc	
920 gagaaggggggaccttggat	
921 gagaaggggggaccttccat	
922 gagaaggggggcagactgtat	
923 tccatgtggggcctgtatgt	
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936 tccatgggggtccatgtatgt	
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938 gctagaggaggatgt	
939 ttttttttttttttttttt	s
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946 ttcccttttttttttttttttttt	s
947 ggggtcatcgatgagggggg s	sos
948 tccatgacgttccatgtacgtt	
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958 tccatgacgttccatgtacgtt	
959 gggggacgtatgtgggggg	sos
960 gggggtcgtacgacgggggg	sos
961 ttttttttttttttttttttttt	po
962 aaaaaaaaaaaaaaaaaaaaaaaa	po
963 CCCCCCCCCCCCCCCCCCCCC	po
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973 ggggtcgtcgacgaggggggg	sos
974 ggggtcgacgtacgtcgagggggg	sos
975 ggggacggtaaccgggtgggggg	sos
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984 tcacgatcgta	s
985 tcagcatcgta	s
986 gggggagcatgtgggggggg	sos
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TABLE 1-continued

SEQ ID NO:	ODN SEQUENCE	BACKBONE
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993	tccataccggtcctgtatgtct	
994	tccataccggtcctaccgggt	s
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996	ggggggacgatcggtgggggg	sos
997	ggg ggg acg atc gtc ggg ggg	sos
998	ggg gga cga tcg tcg ggg ggg	sos
999	aaa gac gtt aaa	po
1000	aaagagcttaaa	po
1001	aaagagzttaaa	po
1002	aaatt <u>gg</u> aaaa	po
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1004	ggggggatcaacgttgggggggg	sos
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1006	ggatccctttagtttactttct	po
1007	ccattccacttctgtattacc	po
1008	tatgttattatcatgtatgtata	po
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1011	atagaaggccctacaccagg	po
1012	ttacaccggctatggaggt	po
1013	ctaaccaggatcaagtctttag	po
1014	cctagactttagtctgggttag	po
1015	tataaagctcgccgacatcg	po
1016	catgtcgacggggcttata	po
1017	tgggtggggggagtaagctc	po
1018	gacgtactccccaccacca	po
1019	gccttcgtatctcggtggga	po
1020	tggacttcttttgcgcgtt	po
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1034	ataagtcatattttggaaactac	
1035	cccaatcaccataggctaaatt	
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1049	ggggacgtcgacgtgggggg	sos
1050	gcacttccgttgcacgttacacggggcggcgttgcgtat	
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1052	cggtcttccatggaaatgtttggacgtgtgac	
1053	tccgtcgagggttaatgt	s
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1059	ggttttttttgttgcgttgcgtt	s
1060	ggttttttttgttgcgttgcgtt	s
1061	ggttttttttgttgcgttgcgtt	s
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TABLE 1-continued

SEQ ID NO:	ODN SEQUENCE	BACKBONE
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1066	tccaaaacttctcaaaatt	s
1067	tactactttataacttttataactt	s
1068	tggtgttgtgttgttgttgtg	s
1069	tttgttgttgttgttgttgttg	s
1070	ggctccggggaggaaatttttgtctat	s
1071	gggacgtatcgccgggggggg	sos
1072	gggtcgtcgacgaggggggg	sos
1073	ggtcgtcgacgaggggggg	sos
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1078	ggggaaaccgcgttgggggggg	sos
1079	ggggacgtatcgatgggggggg	sos
1080	tctgtcgatcgatcgatgggggggg	sos
1081	tctgtccggggaaagt	s
1082	tctgtcgatggggaaagt	s
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1087	tccggggccggggaaagt	s
1088	tccggggccggggaaagt	s
1089	tccggggccggggaaagt	s
1090	ggggggacgttgggggg	s
1091	ggggtttttttttttgggggg	sos
1092	ggggcccccccccccggggggg	sos
1093	ggggtgttgttgttgtgggggg	sos

[0053] In some embodiments, the immunostimulatory nucleic acid is a CpG nucleic acid. CpG sequences, while relatively rare in human DNA are commonly found in the DNA of infectious organisms such as bacteria. The human immune system has apparently evolved to recognize CpG sequences as an early warning sign of infection and to initiate an immediate and powerful immune response against invading pathogens without causing adverse reactions frequently seen with other immune stimulatory agents. Thus CpG containing nucleic acids, relying on this innate immune defense mechanism can utilize a unique and natural pathway for immune therapy. The effects of CpG nucleic acids on immune modulation have been described extensively in published patent applications, such as PCT/US95/01570), PCT/US97/19791, PCT/US98/03678; PCT/US98/10408; PCT/US98/04703; PCT/US99/07335; and PCT/US99/09863. The entire contents of each of these patent applications is hereby incorporated by reference.

[0054] A CpG nucleic acid is a nucleic acid which includes at least one unmethylated CpG dinucleotide. A nucleic acid containing at least one unmethylated CpG dinucleotide is a nucleic acid molecule which contains an unmethylated cytosine in a cytosine-guanine dinucleotide sequence (i.e. "CpG DNA" or DNA containing a 5' cytosine followed by 3' guanosine and linked by a phosphate bond) and activates the immune system. The CpG nucleic acids can be double-stranded or single-stranded. Generally, double-stranded molecules are more stable in vivo, while single-stranded molecules have increased immune activity. Thus in some aspects of the invention it is preferred that the nucleic acid be single stranded and in other aspects it is preferred that the nucleic acid be double stranded. The terms

CpG nucleic acid or CpG oligonucleotide as used herein refer to an immunostimulatory CpG nucleic acid or a nucleic acid unless otherwise indicated. The entire immunostimulatory nucleic acid can be unmethylated or portions may be unmethylated but at least the C of the 5' CG 3' must be unmethylated.

[0055] In one preferred embodiment the invention provides an immunostimulatory nucleic acid which is a CpG nucleic acid represented by at least the formula:

[0056] wherein X_1 , X_2 , X_3 , and X_4 are nucleotides. In one embodiment X_2 is adenine, guanine, cytosine, or thymine. In another embodiment X_3 is cytosine, guanine, adenine, or thymine. In other embodiments X_2 is adenine, guanine, or thymine and X_3 is cytosine, adenine, or thymine.

[0057] In another embodiment the immunostimulatory nucleic acid is an isolated CpG nucleic acid represented by at least the formula:

5'N₁X₁X₂CGX₂X₁N₂3'

[0058] wherein X_1 , X_2 , X_3 , and X_4 are nucleotides and N is any nucleotide and N_1 and N_2 are nucleic acid sequences composed of from about 0-25 N's each. In one embodiment X_1 , X_2 are nucleotides selected from the group consisting of: GpT, GpG, GpA, ApA, ApT, ApG, CpT, CpA, CpG, TpA, TpT, and TpG; and X_3 , X_4 are nucleotides selected from the group consisting of: TpT, ApT, TpG, ApG, CpG, TpC, ApC, CpC, TpA, ApA, and CpA. Preferably X_1 , X_2 are GpA or GpT and X_3 , X_4 are TpT. In other embodiments X_1 or X_2 or both are purines and X_3 or X_4 or both are pyrimidines or X_1 , X_2 are GpA and X_3 or X_4 or both are pyrimidines. In another

not exclusively associated with atopic or allergic symptoms. An "initiator" as used herein refers to a composition or environmental condition which triggers asthma. Initiators include, but are not limited to, allergens, cold temperatures, exercise, viral infections, SO_2 .

[0103] In another aspect the invention provides methods for treating or preventing asthma or allergy in a hypo-responsive subject. As used herein, a hypo-responsive subject is one who has previously failed to respond to a treatment directed at treating or preventing asthma or allergy or one who is at risk of not responding to such a treatment. The treatment directed at treating or preventing asthma or allergy may be an asthma/allergy medicament, in which case the hypo-responsive subject is one who is hypo-responsive to an asthma/allergy medicament.

[0104] Other subjects who are hypo-responsive include those who are refractory to an asthma/allergy medicament. As used herein, the term "refractory" means resistant or failure to yield to treatment. Such subjects may be those who never responded to an asthma/allergy medicament (i.e., subjects who are non-responders), or alternatively, they may be those who at one time responded to an asthma/allergy medicament, but have since that time have become refractory to the medicament. In some embodiments, the subject is one who is refractory to a subset of medicaments. A subset of medicaments is at least one medicament. In some embodiments, a subset refers to 2, 3, 4, 5, 6, 7, 8, 9, or 10 medicaments.

[0105] In other embodiments, hypo-responsive subjects are elderly subjects, regardless of whether they have or have not previously responded to a treatment directed at treating or preventing asthma or allergy. Elderly subjects, even those who have previously responded to such treatment, are considered to be at risk of not responding to a future administration of this treatment. Similarly, neonatal subjects are also considered to be at risk of not responding to treatment directed at treating or preventing asthma or allergy.

[0106] In some embodiments, an immunostimulatory nucleic acid is administered to the hypo-responsive subject without the further administration of an asthma/allergy medicament. In yet other embodiments, an asthma/allergy medicament is administered to the hypo-responsive subject, in which case it may be administered substantially simultaneously (i.e., concurrently with, or following the administration of the immunostimulatory nucleic acid).

[0107] An "asthma/allergy medicament" as used herein is a composition of matter which reduces the symptoms, inhibits the asthmatic or allergic reaction, or prevents the development of an allergic or asthmatic reaction. Various types of medicaments for the treatment of asthma and allergy are described in the Guidelines For The Diagnosis and Management of Asthma, Expert Panel Report 2, NIH Publication No. 97/4051, Jul. 19, 1997, the entire contents of which are incorporated herein by reference. The summary of the medicaments as described in the NIH publication is presented below.

[0108] In most embodiments the asthma/allergy medicament is useful to some degree for treating both asthma and allergy. Some asthma/allergy medicaments are preferably used in combination with the immunostimulatory nucleic acids to treat asthma. These are referred to as asthma

medicaments. Asthma medicaments include, but are not limited, PDE-4 inhibitors, bronchodilator/beta-2 agonists, K⁺ channel openers, VLA-4 antagonists, neurokinin antagonists, TXA2 synthesis inhibitors, xanthanines, arachidonic acid antagonists, 5 lipoxygenase inhibitors, thromboxin A2 receptor antagonists, thromboxane A2 antagonists, inhibitor of 5-lipoxy activation proteins, and protease inhibitors.

[0109] Bronchodilator/beta-2 agonists are a class of compounds which cause bronchodilation or smooth muscle relaxation. Bronchodilator/beta-2 agonists include, but are not limited to, salmeterol, salbutamol, albuterol, terbutaline, D2522/formoterol, fenoterol, bitolterol, pribucrol methylxanthines and orciprenaline. Long-acting β_2 agonists and bronchodilators are compounds which are used for long-term prevention of symptoms in addition to the anti-inflammatory therapies. They function by causing bronchodilation, or smooth muscle relaxation, following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction. These compounds also inhibit mast cell mediator release, decrease vascular permeability and increase mucociliary clearance. Long-acting β_2 agonists include, but are not limited to, salmeterol and albuterol. These compounds are usually used in combination with corticosteroids and generally are not used without any inflammatory therapy. They have been associated with side effects such as tachycardia, skeletal muscle tremor, hypokalemia, and prolongation of Q-Tc interval in overdose.

[0110] Methylxanthines, including for instance theophylline, have been used for long-term control and prevention of symptoms. These compounds cause bronchodilation resulting from phosphodiesterase inhibition and likely adenosine antagonism. It is also believed that these compounds may effect eosinophilic infiltration into bronchial mucosa and decrease T-lymphocyte numbers in the epithelium. Dose-related acute toxicities are a particular problem with these types of compounds. As a result, routine serum concentration must be monitored in order to account for the toxicity and narrow therapeutic range arising from individual differences in metabolic clearance. Side effects include tachycardia, nausea and vomiting, tachyarrhythmias, central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia and hypokalemia. Short-acting β_2 agonists/bronchodilators relax airway smooth muscle, causing the increase in air flow. These types of compounds are a preferred drug for the treatment of acute asthmatic systems. Previously, short-acting β_2 agonists had been prescribed on a regularly-scheduled basis in order to improve overall asthma symptoms. Later reports, however, suggested that regular use of this class of drugs produced significant diminution in asthma control and pulmonary function (Sears, et al. *Lancet*; 336:1391-6, 1990). Other studies showed that regular use of some types of β_2 agonists produced no harmful effects over a four-month period but also produced no demonstrable effects (Drazen, et al., *N. Eng. J. Med.*; 335:841-7, 1996). As a result of these studies, the daily use of short-acting β_2 agonists is not generally recommended. Short-acting β_2 agonists include, but are not limited to, albuterol, bitolterol, pributanol, and terbutaline. Some of the adverse effects associated with the mastration of short-acting β_2 agonists include tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, and hyperglycemia.

agents such as adjuvants to enhance immune responses even further. The immunostimulatory nucleic acid, asthma/allergy medicament and other therapeutic agent may be administered simultaneously or sequentially. When the other therapeutic agents are administered simultaneously they can be administered in the same or separate formulations, but are administered at the same time. The other therapeutic agents are administered sequentially with one another and with the immunostimulatory nucleic acid and asthma/allergy medicament, when the administration of the other therapeutic agents and the immunostimulatory nucleic acid and asthma/allergy medicament is temporally separated. The separation in time between the administration of these compounds may be a matter of minutes or it may be longer. Other therapeutic agents include but are not limited to non-nucleic acid adjuvants, cytokines, antibodies, antigens, etc.

[0160] A "non-nucleic acid adjuvant" is any molecule or compound except for the immunostimulatory nucleic acids described herein which can stimulate the humoral and/or cellular immune response. Non-nucleic acid adjuvants include, for instance, adjuvants that create a depo effect, immune stimulating adjuvants, adjuvants that create a depo effect and stimulate the immune system and mucosal adjuvants.

[0161] An "adjuvant that creates a depo effect" as used herein is an adjuvant that causes an antigen or allergen to be slowly released in the body, thus prolonging the exposure of immune cells to the antigen or allergen. This class of adjuvants includes but is not limited to alum (e.g., aluminum hydroxide, aluminum phosphate); or emulsion-based formulations including mineral oil, non-mineral oil, water-in-oil or oil-in-water-in oil emulsion, oil-in-water emulsions such as Seppic ISA series of Montanide adjuvants (e.g., Montanide ISA 720, AirLiquide, Paris, France); MF-59 (a squalene-in-water emulsion stabilized with Span 85 and Tween 80; Chiron Corporation, Emeryville, Calif.; and PROVAX (an oil-in-water emulsion containing a stabilizing detergent and a micelle-forming agent; IDEC, Pharmaceuticals Corporation, San Diego, Calif.).

[0162] An "immune stimulating adjuvant" is an adjuvant that causes activation of a cell of the immune system. It may, for instance, cause an immune cell to produce and secrete cytokines. This class of adjuvants includes but is not limited to saponins purified from the bark of the *Q. saponaria* tree, such as QS21 (a glycolipid that elutes in the 21st peak with HPLC fractionation; Aquila Biopharmaceuticals, Inc., Worcester, Mass.); poly[di(carboxylatophenoxy)phosphazene (PCPP polymer, Virus Research Institute, USA); derivatives of lipopolysaccharides such as monophosphoryl lipid A (MPL; Ribi ImmunoChem Research, Inc., Hamilton, Mont.), muramyl dipeptide (MDP; Ribi) and threonyl-muramyl dipeptide (t-MDP; Ribi); OM-174 (a glucosamine disaccharide related to lipid A; OM Pharma SA, Meyrin, Switzerland); and Leishmania elongation factor (a purified Leishmania protein; Corixa Corporation, Seattle, Wash.).

[0163] "Adjuvants that create a depo effect and stimulate the immune system" are those compounds which have both of the above-identified functions. This class of adjuvants includes but is not limited to ISCOMS (Immunostimulating complexes which contain mixed saponins, lipids and form virus-sized particles with pores that can hold antigen; CSL, Melbourne, Australia); SB-AS2 (SmithKline Beecham adju-

vant system #2 which is an oil-in-water emulsion containing MPL and QS21; SmithKline Beecham Biologicals [SBB], Rixensart, Belgium); SB-AS4 (SmithKline Beecham adjuvant system #4 which contains alum and MPL; SBB, Belgium); non-ionic block copolymers that form micelles such as CRL 1005 (these contain a linear chain of hydrophobic polyoxpropylene flanked by chains of polyoxyethylene; Vaxcel, Inc., Norcross, Ga.); and Syntex Adjuvant Formulation (SAF, an oil-in-water emulsion containing Tween 80 and a nonionic block copolymer; Syntex Chemicals, Inc., Boulder, Colo.).

[0164] A "non-nucleic acid mucosal adjuvant" as used herein is an adjuvant other than an immunostimulatory nucleic acid that is capable of inducing a mucosal immune response in a subject when administered to a mucosal surface in conjunction with an antigen or allergen. Mucosal adjuvants include but are not limited to Bacterial toxins: e.g., Cholera toxin (CT), CT derivatives including but not limited to CT B subunit (CTB) (Wu et al., 1998; Tochikubo et al., 1998); CTD53 (Val to Asp) (Fontana et al., 1995); CTK97 (Val to Lys) (Fontana et al., 1995); CTK104 (Tyr to Lys) (Fontana et al., 1995); CTD53/K63 (Val to Asp, Ser to Lys) (Fontana et al., 1995); CTH54 (Arg to His) (Fontana et al., 1995); CTN107 (His to Asn) (Fontana et al., 1995); CTE114 (Ser to Glu) (Fontana et al., 1995); CTE112K (Glu to Lys) (Yamamoto et al., 1997a); CTS61F (Ser to Phe) (Yamamoto et al., 1997a, 1997b); CTS106 (Pro to Lys) (Douce et al., 1997; Fontana et al., 1995); and CTK63 (Ser to Lys) (Douce et al., 1997; Fontana et al., 1995), Zonula occludens toxin, zot, *Escherichia coli* heat-labile enterotoxin, Labile Toxin (LT), LT derivatives including but not limited to LT B subunit (LTB) (Verweij et al., 1998); LT7K (Arg to Lys) (Komase et al., 1998; Douce et al., 1995); LT61F (Ser to Phe) (Komase et al., 1998); LT112K (Glu to Lys) (Komase et al., 1998); LT118E (Gly to Glu) (Komase et al., 1998); LT146E (Arg to Glu) (Komase et al., 1998); LT192G (Arg to Gly) (Komase et al., 1998); LTK63 (Ser to Lys) (Marchetti et al., 1998; Douce et al., 1997, 1998; Di Tommaso et al., 1996); and LTR72 (Ala to Arg) (Giuliani et al., 1998), Pertussis toxin, PT (Lycke et al., 1992; Spangler BD, 1992; Freytag and Clements, 1999; Roberts et al., 1995; Wilson et al., 1995) including PT-9K/129G (Roberts et al., 1995; Croplcy et al., 1995); Toxin derivatives (see below) (Holmgren et al., 1993; Verweij et al., 1998; Rappuoli et al., 1995; Freytag and Clements, 1999); Lipid A derivatives (e.g., monophosphoryl lipid A, MPL) (Sasaki et al., 1998; Vancott et al., 1998; Muramyl Dipeptide (MDP) derivatives (Fukushima et al., 1996; Ogawa et al., 1989; Michalek et al., 1983; Morisaki et al., 1983); Bacterial outer membrane proteins (e.g., outer surface protein A (OspA) lipoprotein of *Borrelia burgdorferi*, outer membrane protein of *Neisseria meningitidis*) (Marinaro et al., 1999; Van de Verg et al., 1996); Oil-in-water emulsions (e.g., MF59) (Barchfield et al., 1999; Verschoor et al., 1999; O'Hagan, 1998); Aluminum salts (Isaka et al., 1998, 1999); and Saponins (e.g., QS21) Aquila Biopharmaceuticals, Inc., Worcester, Mass.) (Sasaki et al., 1998; MacNeal et al., 1998), ISCOMS, MF-59 (a squalene-in-water emulsion stabilized with Span 85 and Tween 80; Chiron Corporation, Emeryville, Calif.); the Seppic ISA series of Montanide adjuvants (e.g., Montanide ISA 720; AirLiquide, Paris, France); PROVAX (an oil-in-water emulsion containing a stabilizing detergent and a micelle-forming agent; IDEC Pharmaceuticals Corporation, San Diego, Calif.); Syntex Adjuvant Formulation (SAF);

Syntex Chemicals, Inc., Boulder, Colo.); poly[di(carboxy-latophenoxy)phosphazene (PCPP polymer; Virus Research Institute, USA) and Leishmania elongation factor (Corixa Corporation, Seattle, Wash.).

[0165] Immune responses can also be induced or augmented by the co-administration or co-linear expression of cytokines (Bueler & Mulligan, 1996; Chow et al., 1997; Geissler et al., 1997; Iwasaki et al., 1997; Kim et al., 1997) or B-7 co-stimulatory molecules (Iwasaki et al., 1997; Tsuji et al., 1997) with the immunostimulatory nucleic acids and asthma/allergy medicaments. The cytokines can be administered directly with immunostimulatory nucleic acids or may be administered in the form of a nucleic acid vector that encodes the cytokine, such that the cytokine can be expressed in vivo. In one embodiment, the cytokine is administered in the form of a plasmid expression vector. The term "cytokine" is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators at nano- to picomolar concentrations and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment. Examples of cytokines include, but are not limited to IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-15, IL-18 granulocyte-macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), interferon- γ (IFN- γ), IFN- α , tumor necrosis factor (TNF), TGF- β , FLT-3 ligand, and CD40 ligand. Cytokines play a role in directing the T cell response. Helper (CD4+) T cells orchestrate the immune response of mammals through production of soluble factors that act on other immune system cells, including other T cells. Most mature CD4+ T helper cells express one of two cytokine profiles: Th1 or Th2. In some embodiments it is preferred that the cytokine be a Th1 cytokine.

[0166] The term "effective amount" of an immunostimulatory nucleic acid and an asthma/allergy medicament refers to the amount necessary or sufficient to realize a desired biologic effect. For example, an effective amount of an immunostimulatory nucleic acid and an asthma/allergy medicament for treating or preventing asthma or preventing is that amount necessary to prevent the development of IgE in response to an allergen or initiator upon exposure to the allergen or initiator is that amount necessary to cause the shift from Th2 to Th1 response in response to an allergen or initiator.

[0167] Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is entirely effective to treat the particular subject. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular immunostimulatory nucleic acid or asthma/allergy medicament being administered (e.g. the type of nucleic acid, i.e. a CpG nucleic acid, the number of unmethylated CpG motifs or their location in the nucleic acid, the degree of modification of the backbone to the oligonucleotide the type of medicament), the size of the subject, or the severity of the disease

or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular immunostimulatory nucleic acid and/or asthma/allergy medicament and/or other therapeutic agent without necessitating undue experimentation.

[0168] Depending upon the aspect of the invention, the immunostimulatory nucleic acid and asthma/allergy medicament may be administered in a synergistic amount effective to treat or prevent asthma or allergy. A synergistic amount is that amount which produces a physiological response that is greater than the sum of the individual effects of either the immunostimulatory nucleic acid or the asthma/allergy medicament alone. For instance, in some embodiments of the invention, the physiological effect is a reduction in IgE levels. A synergistic amount is that amount which produces a reduction in IgE that is greater than the sum of the IgE reduced by either the immunostimulatory nucleic acid or the asthma/allergy medicament alone. In other embodiments, the physiological result is a shift from Th2 cytokines, such as IL-4 and IL-5, to Th1 cytokines, such as IFN- γ and IL-12. The synergistic amount in this case is that amount which produces the shift to a Th1 cytokine that is greater than the sum of the shift produced by either the immunostimulatory nucleic acid or the asthma/allergy medicament alone. In other embodiments the physiological result is a decrease in eosinophilia, hyperreactivity, or lung function.

[0169] In some embodiments of the invention, the immunostimulatory nucleic acid is administered in an effective amount for preventing bacterial or viral infection. Immunostimulatory nucleic acids are known to be useful for preventing bacterial and viral infections. Bacterial and viral infections exacerbate and/or induce allergy and/or asthma. In this aspect of the invention, the immunostimulatory nucleic acid is administered to the subject in an amount effective to prevent bacterial and viral infection and the asthma/allergy medicament is administered to the subject when symptoms of allergy or asthma appear. Thus, the immunostimulatory nucleic acid is administered to the subject and then the asthma/allergy medicament is subsequently administered to the subject or they are administered together at the same time. This method is particularly useful in subjects such as children and immunocompromised subjects, or elderly subjects, who are particularly susceptible to bacterial or viral disease.

[0170] In aspects of the invention directed at treating subjects in anticipation of an asthmatic or allergic event or season (e.g., in anticipation of the hay-fever season), the subjects may be administered an immunostimulatory nucleic acid in an effective amount for preventing the asthma or allergy. In related embodiments of this method, an asthma/allergy medicament is also administered to the subject. In these latter instances, the amount of the immunostimulatory nucleic acid administered may be that amount necessary to reduce the effective dose of the asthma/allergy medicament which is required to treat or prevent the asthma or allergy.

[0171] Thus, in these embodiments, the immunostimulatory nucleic acid potentiates the effect of the asthma/allergy medicament. The ability to potentiate the effect of an asthma/allergy medicament is useful since it allows for a reduction in the administered dose of an asthma/allergy medicament with the same or better therapeutic result. As an